Vascular Function

Blood Flow: Relationship between flow (F), pressure (P) & resistance (R) in blood vessels: *Poiseuille-Hagen Formula:*

- Flow means volume of fluid that crosses a point per unit time (e.g., cm^3/second).
- Blood flow in total circulation → amount of blood pumped into aorta/min → COP
- Flow ∝ effective perfusion pressure or "pressure gradient (ΔP → mean pressure in arterial end - mean pressure at venous end of the vessel $P_1 - P_2$)"
- Flow is inversely proportional to resistance of the vessel to blood flow (R).
- Therefore; $F = \Delta P \div R$

Resistance to blood flow is determined by:

1- Radius of the vessel (r): $R \propto 1/r^4$

2- Length of the vessel (L): $R \propto L$

3- Viscosity of blood (η): $R \propto \eta$

Poiseuille-Hagen formula describes the relation between flow in a long narrow tube (F), viscosity of fluid (η), length of tube (L) and radius of tube (r): $F = \pi \Delta P r^4 / 8 \eta L$

- **Effect of radius on resistance:**

  Resistance, and consequently blood flow, is markedly affected by radius of vessel.

  +++ vessel radius by 20% → ---- resistance by 50% & the flow is almost doubled.

- **Effect of viscosity on resistance:**

  - Viscosity of blood depends on hematocrit value.

  - Peripheral resistance is only affected by large changes in HV.

  - +++ IGs in some diseases & rigid RBCs in hereditary spherocytosis → +++ viscosity

- **Effect of pressure on vascular resistance:**

  Due to the elasticity of blood vessels pressure tends to distend the vessel, increase its radius and decrease resistance to flow. This means that the same pressure gradient can produce higher flow in an elastic vessel than in a rigid one

Calculation of total peripheral resistance of vascular system:

Total blood flow in CVS is the cardiac output (COP). It occurs under the effect of a pressure gradient between mean arterial pressure (MAP) and right atrial pressure (RAP).

COP = (MAP – RAP) / TPR

TPR = (MAP – RAP) / COP = (90 – 0) / 5 **TPR = 18 mmHg/L/min.**

Calculation of resistance of pulmonary circulation (PulR):

Total blood flow in pulmonary circulation = cardiac output (COP). It occurs under effect of pressure gradient between mean pulmonary pressure (MPP) and left atrial pressure (LAP).

PulR = (MPP – LAP) / COP = (15 – 8) / 5 PulR = 1.4 mmHg/L/min

Laminar (Streamline) Flow:

- Within the blood vessels, blood flows in layers.
- The layer in contact with the wall is almost stationary.
- The velocity of flow of the next layer is higher.
- Maximum velocity of flow occurs at the center of the vessel.
- Flow is laminar up to a certain critical velocity above which flow becomes turbulent
- **Turbulent flow means that molecules of the fluid move in different directions forming eddy currents. This can occur:**
  - very high velocity of blood flow
  - sudden change of diameter of the vessel
  - ------ viscosity of blood (anemia)
  - sharp turn in direction of flow
  - blood passes over rough area of the blood vessel
- Laminar flow is silent, but turbulent flow creates sounds (murmurs).
- Turbulent flow meets greater resistance than laminar flow.
- **Turbulence occurs in anemia (low viscosity and high blood velocity)**

Law of La Place

Wall tension (T) in thin-walled cylinder (blood Vessel) = transmural pressure (P) x radius (r):

T = Pr or, P = T/r (Tissue pressure in body is low ∴ P = pressure inside the vessel).

- In a thin-walled asymmetric viscus: **$P = T (1/r_1 + 1/r_2)$,**
  where r_1 & r_2 are the 2 principle radii of the viscus
- In a sphere (symmetric: $r_1 = r_2$) ∴ **P = 2T/r**
- In a cylinder as blood vessel, one radius is infinite ($1/\infty$ = zero): **P = T/r**
- It quantifies the tension generated in vessel wall to balance the distending pressure
- It calculates the pressure generated inside the ventricle due to increased wall tension when the ventricle contract

Physiological importance of La Place law (P = 2T/ r):

- It explains how capillaries due to their very small radius can withstand high pressure. In capillaries (small radius), the developed wall tension necessary to balance the distending pressure, will be small (T=Pr)
- A dilated ventricle (heart diseases) has to generate more tension during contraction to elevate intraventricular pressure. Because P = T/r, so, if +++ radius (dilated heart) then tension should proportionately increase to generate same pressure needed to open semilunar valve.

- As urinary bladder fills, the tension in the wall rises, but so does the radius → slight increase in pressure until it is relatively full. At a certain volume, T markedly increases & intravesical pressure rises sharply.

Venous Circulation

Venous Pressure:

I- Central Venous Pressure (CVP) "Right Atrial Pressure":

- Normally equals 0-2 mm Hg.
- **Significance:**

1. It is the main force for ventricular filling.
2. Difference between CVP & mean systemic filling pressure (7-8 mm Hg) = gradient for VR
3. It is considered an index of blood volume.
4. CVP is decreased in hemorrhage (---blood volume → --- VR → --- CVP).
5. CVP is increased in right-sided heart failure (+++ blood in right atrium → +++ CVP).

II- Peripheral venous pressure:

- In recumbent person, pressure in small venules = 8-12 mmHg; in large veins outside the thorax = 5-6 mmHg & in major veins entering the right atrium = 4-5 mmHg above CVP.
- This low value of venous pressure is due to the little resistance to blood flow in veins.

Venous Pressure (Pv) is determined by two factors:

1- Venous blood volume (Vv).

2- Compliance of veins (Cv), determined mainly by venous tone. Sympathetic stimulation → +++ venous tone & ---- compliance of vein

Venous pressure is affected by the following factors:

1- **Cardiac output:** --- CO → blood accumulate in venous circulation → +++ venous blood volume & +++ Pv

2- **Total blood volume:** +++ blood volume (renal failure) → +++ venous volume & +++ Pv; ---- blood volume (hemorrhage) → ---- venous volume & ---- Pv

3- **Venous tone:** contraction of smooth muscles of veins (+++ sympathetic) → ---- venous compliance & +++ Pv

4- **Arteriolar dilation** in skeletal muscles during exercise → +++ blood flow to veins → +++ venous volume & +++ Pv

5- **Effect of Gravity on Venous Pressure:**

In upright position, pressure in peripheral veins changes:

a- Below the level of right atrium: +++ pressure by 0.77mmHg for each 1cm (80 mmHg in leg veins to during standing → edema & varicose veins)

b- Above the level of right atrium: --- pressure by 0.77mmHg for each 1cm; → Neck veins are collapsed. (Pressure in dural sinuses is sub-atmospheric (have rigid walls, don't collapse). If opened dural sinuses (neuro-surgical operations) while patient is seated → air sucked in sinuses → fatal air embolism).

Venous Return (VR) & its Regulation

Venous return is determined by Ohm's law:

$$\text{Flow (F)} = \frac{\text{Pressure Gradient}}{\text{Resistance}} \qquad \text{Venous Return (VR)} = \frac{\text{MSFP} - \text{RAP}}{\text{RVR}}$$

1- Mean systemic filling pressure (MSFP):

a. It reflects the degree of distension of the circulation with blood.

b. MSFP = force that drives blood back to heart = pressure that drives the VR.

c. MSFP = pressure present all over the systemic circulation if the heart stops pumping.

d. If the cardiac output decreases gradually:

i. Mean arterial pressure gradually decreases.

ii. Right atrial pressure gradually rises (blood is backing up in venous side)

e. When the heart stops pumping → zero CO → arterial pressure = RAP = pressure at zero blood flow = MSFP = 6-8 mmHg normally

f. MSFP reflects the relationship between two factors:

i. Blood volume. ii. Capacity mainly of veins.

---- blood volume (hemorrhage) or +++ capacity of circulation (----sympathetic) → ----MSFP

+++blood volume (renal failure) or ----capacity of circulation (+++sympathetic) → +++ MSFP

2- Right atrial pressure (RAP):

a. VR depends on the difference between MSFP & RAP → "**pressure gradient for VR**"

b. +++ right atrial pressure → ----- venous return.

3- Resistance to venous return (RVR):

$$\text{RVR} = \frac{\text{MSFP} - \text{RAP}}{\text{VR}} = 7 - 0 / 5 = 1.4 \text{ mmH/L/min}$$

Venous Return Curve: describes the relationship between RAP & VR.

A- Effect of changes in RAP on venous return curve:

- +++ RAP → ---- VR; When the RAP reaches 7 mmHg → ----VR to zero (VR stops):

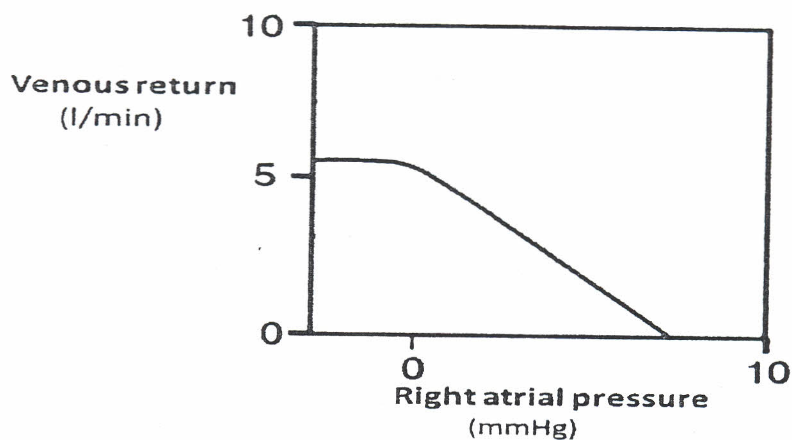


Figure (73): Venous return curve.

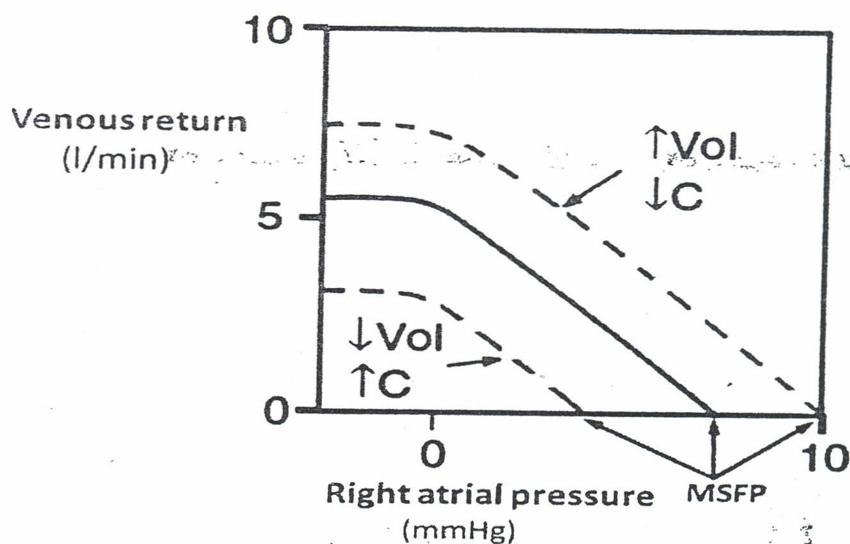
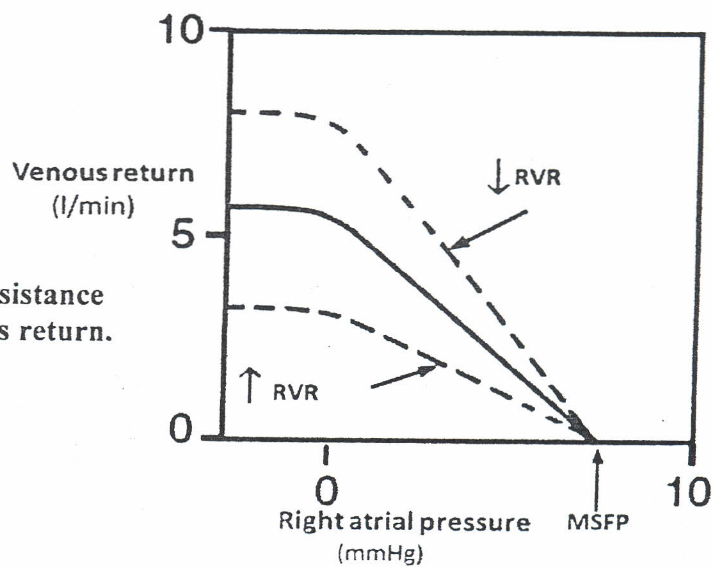


Figure (74): Effect of changing MSFP (by changing blood volume "vol" or capacity of the circulatory "C") on venous return.

Figure (75): Effect of changing resistance to venous return (RVR) on venous return.



$$\text{Venous Return (VR)} = \frac{\text{MSFP - RAP}}{\text{RVR}}$$

VR = MSFP (7) - RAP (7) / RVR = 0 / RVR = zero

- The maximum value that the RAP can rise to, is the MSFP
- -----RAP → +++ VR
- If RAP decreases to -1 mmHg or less → VR reaches a plateau (collapse of thoracic veins)

B- Effect of changes in MSFP on venous return curve:

- +++ **MSFP** (+++blood volume or ----capacity of circulation) → shift of VR curve up & right (at any RAP, **higher VR** is achieved)
- -----**MSFP** → shift of VR curve down & left (at any RAP, **lower VR** is achieved)

C- Effect of changes in RVR on venous return curve:

- ----**RVR** → +++ slope of VR curve (for same RAP → +++ **VR**)
- +++**RVR** → ----- slope of VR curve (for same RAP → ---- **VR**)
- Changes in RVR don't affect the value of MSFP

Mechanisms that help venous return against gravity:

1. Thoracic Pump:

During inspiration	During expiration
a. IPP falls from –4 to –8 mmHg → --- pressure in intrathoracic veins b. Diaphragmatic descent → +++ intra-abdominal pressure from 5 to 6 mmHg → +++ pressure in abdominal veins c. +++ the gradient between abdominal & thoracic veins = 6 - (-8) = 14 mm Hg. This helps venous return towards the heart.	Pressure gradient = 5 – (-4) = 9 mmHg → lower VR during expiration

2. Heartbeat Effects:

▪ **Atrial suction:**	▪ **Ventricular suction:**
During rapid ejection phase, atrioventricular ring is pulled down → sharp drop of atrial pressure → suck blood into atria from great veins	During rapid filling phase, opening of tricuspid valve → low ventricular pressure suck blood from atria & veins

3. Muscle Pump:

Contraction of skeletal muscles surrounding limb veins during activity compresses the veins.

4. The Venous Valves

Venous valves → allow blood flow towards the heart but prevent retrograde flow. Incompetent valves (varicose veins) → stasis of blood in lower limb.

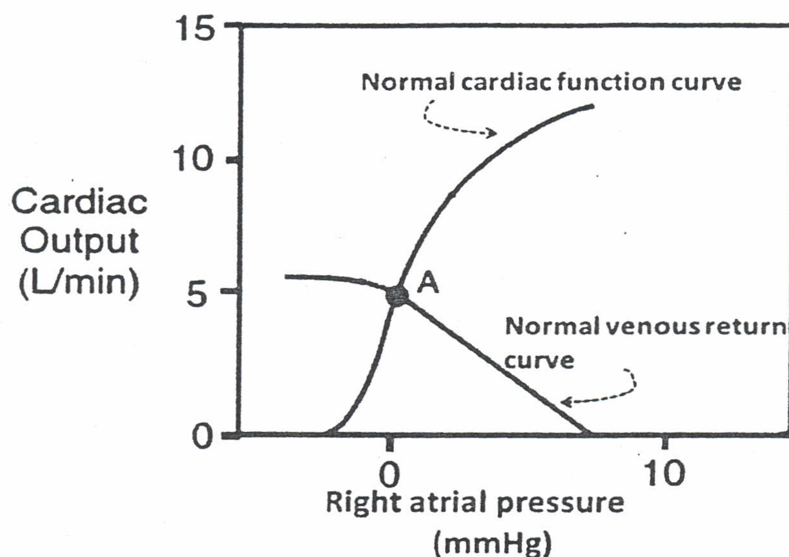


Figure (76): Cardiac function curve and venous return curve. Intercept point "A" represents steady state operation of the cardiovascular system.

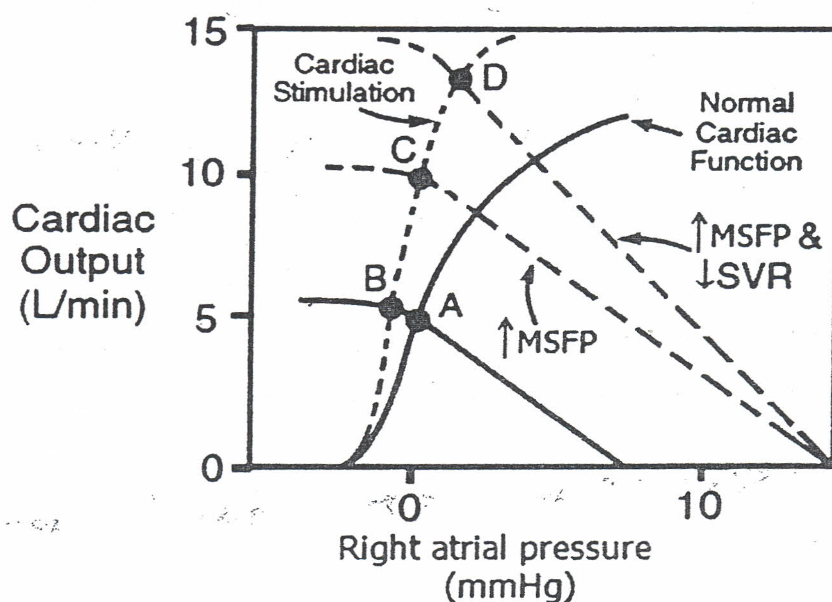


Figure (77): Interaction between cardiac function and peripheral vascular function. The degree of increase in cardiac output due to cardiac stimulation (point B) depends largely on the simultaneous changes in vascular function (MSFP and SVR, points C & D).

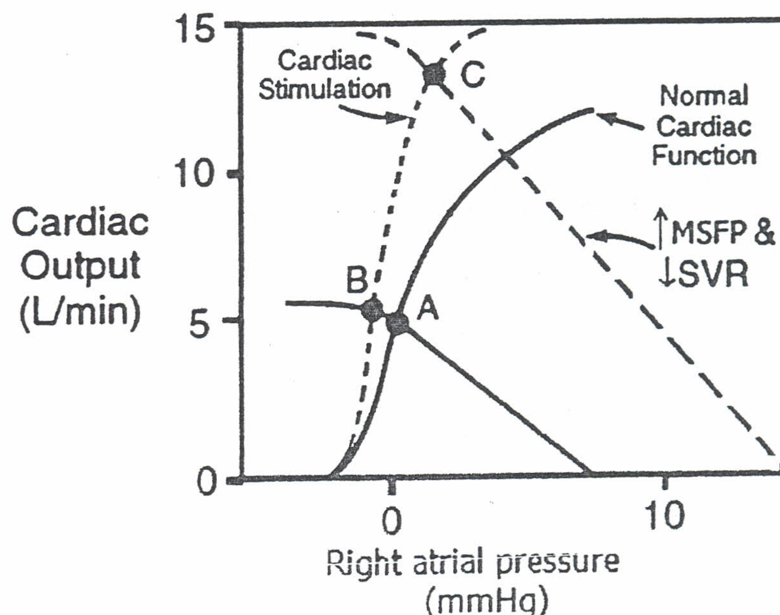


Figure (78): Interaction between cardiac function and peripheral vascular factors during muscular exercise

Interaction between Cardiac Factors & Peripheral Vascular Factors in the Control of Cardiac Output

This interaction can be clearly studied if we **super-impose** two curves:

- **CO curve**: describes cardiac factors that control CO (preload, afterload, inotropy, HR)
- **VR curve**: describes peripheral vascular factors that control VR (MSFP, RVR, RAP)

<u>Intercept point of CO & VR curves (point A)= steady state of cardiovascular system</u>

- Venous return = cardiac output = 5 L/min.
- Right atrial pressure is the same for CO & for VR back = 0 mmHg.

1- What happens when +++ the pumping ability of the heart (+ve inotropics as digitalis)?

a. +++ only the cardiac inotropy → shift the CO curve up & left → +++ CO a little. Due to lower RAP → ---- preload → limit the ability of the heart to increase its output

b. The degree to which CO will increase is largely determined by the conditions of the circulation (described by VR curve).

c. If at the same time we +++ the MSFP → VR curve is shifted up & right → +++ CO to a much higher value (RAP is almost not changed)

d. If at the same time we ----- the RVR → VR curve is shifted more to the right → +++ CO even more (slight +++ in RAP)

2- What happens during muscular exercise?

Cardiovascular responses to exercise:

Muscular exercise → ++++sympathetic → **shift the cardiac function curve up & left:**

a- +++heart rate (impulses from cerebral cortex or from peripheral receptors in muscles).

b- +++inotropy and heart rate.

c- ----total peripheral resistance (+++ VD metabolites; +++ cholinergic sympathetic VD).

This alone can only increase CO a little

During exercise, **VR curve shifts up & right** (+++VR) → +++ CO to higher level;

<u>+++ in VR during exercise:</u>

a. +++ MSFP: +++ sympathetic → contraction of veins

b. +++ muscle pumping action & thoracic & cardiac suction mechanisms

c. Arteriolar VD in muscles → rapid flow of blood from arterial to venous side → +++ VR

d. ----RVR: skeletal muscle vessels are dilated by VD metabolites

Conclusion:

Cardiac stimulation has only a little effect on CO if acting alone. However, if +++ VR by ---- venous capacity & systemic vascular resistance, CO is able to increase to much higher levels.

Capillary Circulation

Equilibrium with Interstitial Fluid

1- Diffusion: most important mechanism for exchange across capillary wall

The rate of diffusion depends on:

a- **Capillary permeability:** discontinuous are more permeable than fenestrated than continuous capillaries. Capillary permeability can change (+++ during inflammation)

b- **Factors related to the substance:**

- concentration gradient, which is directly proportional to rate of diffusion
- Lipid solubility: the more the lipid soluble substance, the more its rate of diffusion
- Molecular size: the smaller the size of a substance, the more its rate of diffusion

2. Trans-Capillary Filtration (Bulk flow):

"Starling Forces" depends on balance of hydrostatic & osmotic pressure gradients:

- **Mean forces tending to move fluid out from capillaries into interstitial space:**
  - Capillary hydrostatic pressure (P_c)
  - Interstitial colloid osmotic pressure (π_i).
- **Mean forces tending to move fluid into capillaries from interstitial space:**
  - Interstitial hydrostatic pressure (P_i)
  - Capillary colloid osmotic pressure (π_c)

Fluid movement $= k\ [\ (P_c + \pi_i) - (P_i + \pi_c)\ ]$

- Interstitial colloid osmotic pressure (π_i) is usually very small and can be ignored.
- Capillary filtration coefficient (k) is proportionate to permeability & surface area.

- **Along a muscle capillary the net force is as follows:**
  - At arteriolar end: (37 + 0) – (1 + 25) = 11 mmHg

Fluid moves out from capillary into the interstitial space under a force of 11 mmHg.

  - At venular end: (17 + 0) – (1 + 25) = - 9 mmHg.

Fluid moves into capillary from the interstitial space under a force of 9 mmHg.

- **Balance of Starling forces is different in other capillaries:**
  a. Fluid moves out along the entire length of capillaries in renal glomeruli.
  b. Fluid moves in along the entire length of capillaries in intestines and lungs.
- **24 L of fluid are filtered through capillaries per day** (0.3% of COP), 85% of filtered fluid is reabsorbed into capillaries & 15% returns to circulation via lymphatics.

3. Vesicular Transport:

- Large lipid-insoluble molecules (proteins) are transported across endothelial cells.

Edema:

Abnormal large accumulation of ISF; mainly in dependent parts (lower limbs in standing position, and back in recumbent position)

Causes of increased ISF volume and edema:

1- Increased Filtration Pressure:

- Arteriolar dilation.
- Venular constriction.
- +++ venous pressure (effect of gravity, +++ ECF, incompetent venous valves, venous obstruction & heart failure.)

2- Decreased Osmotic Pressure Gradient Across Capillary:

- Decreased plasma protein level
  - nutritional edema,
  - liver cirrhosis (--- plasma protein synthesis)
  - kidney diseases as nephrosis (loss of plasma protein in urine.)
- Accumulation of osmotically active substances in interstitial space.

3- Increased Capillary Permeability:

- Substance P.
- Histamine.
- Kinins.

4- Inadequate Lymph Flow:

Lymphatic obstruction (elephantiasis) → high protein content fluid, inflammation & fibrosis of ISF → non-pitting edema

Regulation of the Diameter of Arterioles

I- Auto-regulation

Intrinsic capacity of vascular beds to compensate for moderate changes in perfusion pressure by changing vascular resistance so that blood flow remains constant

It is well developed in the kidneys.

A- Myogenic auto-regulation:	B- Metabolic auto-regulation:
Aim: maintain constant blood flow to an organ in spite of increase in its perfusion pressure. **Mechanism:** +++ perfusion pressure → initial +++ in blood flow → distended blood vessels → stretched vascular smooth muscle	**Aim:** maintain constant blood flow to an organ in spite of a decrease in its perfusion pressure. **Mechanism:** ---- perfusion pressure → initial ---- in blood flow → +++ VD metabolites → relaxation of arterioles & pre-capillary sphincters → --- resistance → +++ blood flow. **Vasodilator Metabolites:**

cells VSMCs → +++ Ca^{+2} entry → contraction of VSMCs → VC → +++ resistance → --- flow nearly to its initial value (intrinsic contractile response of VSMCs to stretch)	1. --- O_2 (hypoxia) 2. +++ CO_2 (hypercapnia) 3. +++ body t° 4. +++ K^+ ions 5. +++ osmolarity 6. Adenosine in cardiac muscle 7. Histamine in injured tissues 8. +++ H^+ (acidosis) by acidic metabolites (lactic acid)

Active hyperemia:	Reactive hyperemia:
• +++ blood flow to active tissues • +++ tissue activity → +++ VD metabolites → VD → +++ blood flow	• +++ blood flow to a region when its circulation is reestablished after a period of occlusion. • Occluded blood supply to a limb → hypoxia → +++ VD metabolites→ arteriolar VD distal to occlusion → +++ blood flow when restored circulation → warm limb & red skin

II- Substances secreted by the Endothelium

1) Nitric oxide (NO)

Synthesis: L-arginine in endothelial cells by endothelial NO synthase (eNOS) enzyme

Stimulators: - Acetylcholine - Bradykinin - Shear stress

Mechanism: +++ guanylate cyclase in VSMCs (paracrine action) → +++ cGMP → VD

Actions: VD of coronary, cerebral & pulmonary vessels

- VD of penile arterioles (erection)
- Continuous release of NO → normal ABP (--- NO in hypertensive patient)

2) Endothelin-1: ET-1

Synthesis: ET-1: by endothelial cells → most potent VC agent yet known (1ry type)

ET-2: in kidneys & intestine

ET-3: mainly in brain

ET-receptors: (ET_A) specific for ET-1.

(ET_B) can bind ET-1, ET-2, ET-3

Mechanism: ET binds to ET_A receptors on VSMCs → +++ Ca^{2+} influx → VSMC contraction →VC

ET binds to ET_B receptor on endothelial cells → Release of NO → VD that modulates ET vasoconstrictor effect

Stimulators: - Angiotensin II. – Catecholamines - Vasopressin

- Hypoxia - Shear stress - Thrombin

Inhibitors: - NO - Prostacyclin - ANP

Actions: - VC of veins more than arterioles

- Strong coronary VC
- Pulmonary VC
- Renal VC & --- GFR
- +ve chronotropic & inotropic effect
- +++ catecholamines, ANP, renin & aldosterone

3) Prostacyclin

Synthesis: in endothelial cells from arachidonic acid

Actions: 1- VD

2- --- platelet aggregation

3- facilitates NO release → potentiates its effect onVSMC

III. Systemic Regulation by Hormones

A-Vasoconstrictor hormones

1) Vasopressin

Synthesis: synthesized in hypothalamus and stored in posterior pituitary gland

Stimulators: 1.Hypovolemia, hypotension (Hemorrhage & dehydration)

2.+++ ECF osmolarity

3.AngiotensinII

Actions: 1. Decreases water excretion by kidney via V_2 receptor (anti-diuretic hormone)

2. Strong VC effect via V_1 receptor.

2) Catecholamines

Synthesis: Secreted from adrenal medulla (epinephrine & norepinephrine). (NE is also secreted by postganglionic sympathetic nerves)

Stimulators: 1. +++ sympathetic, stress

2. Hypoglycemia & cold

Actions: Vascular effects of epinephrine:

a.VD of vessels in skeletal ms & liver via β_2 receptors.

b. This action overbalances the VC effects of epinephrine (α_1) in other places.

c. --- the total peripheral resistance (TPR)

Vascular effects of norepinephrine: VC (α_1 receptors)

3) AngiotensinII (Renin-Angiotensin-System RAS)

Synthesis:

1. Renin (proteolytic enzyme) is secreted from juxta-glomerular apparatus in kidney
2. Renin activates hepatic angiotensinogen into Angiotensin-I (decapeptide)
3. Angiotensin converting enzyme (ACE) changes Ang-I into Ang-II (octapeptide).
4. ACE is found in endothelial cells of blood vessel including lung vessels.

10% of ACE is freely circulating in blood & 90% local as tissue membrane bound enzyme

Stimulators: Increased Renin secretion in:

- Hypovolemia and Hypotension.
- Hypoxia → Renal ischemia (renal artery stenosis)
- Hyponatremia
- Sympathetic stimulation (β_1)

Receptors:

a. AT_1 receptor: widespread (most of Ang-II actions)

b. AT_2 receptor: limited in adults.

Actions: Actions mediated via AT1:

1. Inhibition of renin secretion.
2. Peripheral VC of arterioles & veins.
3. +++ Na^+ reabsorption by direct action on distal renal tubules.
4. +++ Aldosterone from adrenal cortex → +++ Na^+ reabsorption by distal tubules
5. +++ Sympathetic, catecholamine secretion
6. Vasopressin secretion (--- water loss in urine)
7. +++ thirst center → +++ water intake

Actions mediated via AT2: (counter-balances the effects of AT_1 receptor)

1. Vasodilatation.
2. Diuresis (+++ renal water excretion)
3. Natriuresis (+++ renal Na^+ excretion)
4. Apoptosis (programmed cell death).

Drugs:

1. Angiotensin-converting enzyme inhibitors (ACE-Is)
2. Angiotensin receptor blockers (ARBs) → block the AT_1 receptor.

B- Vasodilator hormones

1) Kinins: present mainly in tissues, (small amounts are found in blood)

Types:

1. Bradykinin (nonapeptide 9aa)
2. **kallidin** (decapeptide 10aa)

Synthesis: 1. Tissue kallikrein (protease) acts on high-molecular-weight HMW & LMW kininogens→ lysylbradykinin.

2. Plasma kallikrein (protease): acts on HMW kininogen → bradykinin

Receptors: B_1 and B_2 receptors

Actions: Kinins on B_2 receptors have the following functions (like histamine):

1. Relax VSMCs, --- ABP via +++ NO
2. Contraction of visceral plain ms
3. Increase capillary permeability
4. Positive chemotaxic effect
5. ----thrombin-induced platelets aggregation.
6. +++ release of tissue plasminogen activator (tPA) from endothelial cells

Kinins acting on B_1 receptors: stimulate pain receptors.

Metabolism: Kininase I & II enzymes break Kinins into inactive fragments.

Kininase II is same as ACE.... Thus, ACE inhibitors → ---- kininase → +++ kinins → ----ABP

2) Natriuretic hormones:

Synthesis: a. Atrial natriuretic peptide (ANP) → by atrial myocytes

b. Brain natriuretic peptide (BNP) → by ventricular myocytes & brain.

c. C-type natriuretic peptide (CNP) → endothelial cells, brain, kidney

Receptors: a. NPR-A: greatest affinity for ANP.

b. NPR-B: greatest affinity for CNP.

c. NPR-C: bind the 3 natriuretic peptide

Secretion is increased by:

1- Stretch of atrial muscle fibers: +++ ECF (ingestion of high-salt diet & immersion in water up to neck) → +++ VR & CVP.

2- +++ Na^+ concentration in ECF.

3- +++ sympathetic ß-adrenoceptors.

4- Angiotensin-II.

5- Endothelin.

Actions: Counter the ABP-raising effects of RAS; --- blood volume → ---CVP, COP & ABP:

Vascular actions: 1. Relaxation of VSMCs by +++ cGMP.

2. --- the VC effect of catecholamines

3. --- the VC effect of angiotensin II.

Renal actions: 1. +++ Na^+ excretion.

2. --- the conversion of pro-renin to renin

3. --- aldosterone action (--- $Na^+/K^+ATPase$)

Adrenal action: --- aldosterone secretion by adrenal cortex

Drugs: Natriuretic peptides are inactivated by "**neutral endopeptidase**". Drugs that inhibit this enzyme → +++ ANP → treatment of heart failure & hypertension

Regulation of Arterial Blood Pressure

A- Nervous Regulation of Arterial Blood Pressure

Rapidly induced mechanisms(sec to few min)

Centers of rapidly induced reflexes are present in medulla oblongata.

Area	Vasomotor area (VMA)	Cardiac inhibitory area (CIA)
Site	rostral ventrolateral medulla (RVLM)	dorsal motor nucleus (DMN) of vagus & nucleus ambiguous
Mediate	sympathetic discharge to blood vessels & heart	vagal discharge to the heart
Send impulses to	sympathetic preganglionic LHCs → postganglionic fibers → heart, blood vessels	Parasympathetic vagal neurons → innervate the heart
Receive	inhibitory fibers from nucleus tractus solitarius	excitatory fibers from NTS
Stimulation	+++ ABP through: 1. Arteriolar VC (vasomotor tone) → ++ TPR 2. Venoconstriction → +++ VR and COP 3. +++ HR & SV → +++ COP. 4. Associated --- in tonic vagal discharge	--- heart rate & COP (Afferents that +++ VMA will --- CIA at same time & vice versa)

Afferents to cardiovascular centers come from the following:

I.Arterial baroreceptors (high-pressure baroreceptors)

Nature: mechanical stretch receptors, act as "pressure sensors" that monitor ABP.

Site: 1. Aortic arch.

2. Carotid sinus (small dilation of internal carotid artery)

Innervation: buffer nerves which end in NTS:

1. Carotid sinus Hering's nerve, branch of glossopharyngeal nerve: from carotid sinus
2. Aortic nerve (branch of vagus): from aortic baroreceptors

Stimulation:

1. Arterial blood pressure: threshold for stimulation of baroreceptors = 50 mmHg

   Higher pressure → +++discharge → Maximal at 160 mmHg
2. Pulse pressure: higher pulse pressure causes more stimulation.

Function: Baroreceptor Reflex:

To compensate for sudden changes in ABP e.g. change in posture or hemorrhage.

1. **At normal level of MAP (90 mmHg):**

   Stimulated baroreceptors send low rate tonic impulses to +++NTS which send:

   a- Inhibitory signals to VMA.

   b- Excitatory signals to CIA.

2. **When ABP increases:**

   Increased tonic discharge from baroreceptors to NTS lead to:

   a- More ---- of VMA → --- sympathetic →---HR, SV, COP & VD → --- ABP to normal

   b- More +++ of CIA → +++ vagal tone →--- HR & COP→--- ABP back to normal

3. **When arterial blood pressure decreases:**

   Decreased tonic discharge from baroreceptors to NTS lead to:

   a- Less ---- VMA → +++sympathetic → +++ HR, SV, COP & VC → +++ABP to normal

   b- Less +++ of CIA → --- vagal tone to heart → +++ HR & COP → +++ ABP to normal

Resetting of baroreceptor reflex: sustained +++ of ABP for long time → --- baroreceptor reflex sensitivity → it will function to maintain ABP at this higher level (insignificant role in long-term regulation of ABP = defense against hypertension).

Carotid Sinus Syndrome: Some people have sensitive carotid sinus baroreceptors; Application of external pressure to carotid sinus (tight collar or shaving) → +++ reflex → --- ABP → cerebral ischemia & fainting; treated by Denervation of carotid sinus

II. Cardio-pulmonary stretch receptors *(Volume / Atrial / low-pressure receptors / Atrial baroreceptors)*

Nature: Stretch receptors present in low-pressure side of the circulation.

Site: 1. In right and left atrial walls at the entrance of SVC & IVC,

2. In pulmonary veins wall & pulmonary circulation.

Stimulation: 1. Distension of atrial walls.

2. +++ VR, CVP or blood volume → +++ their discharge.

3. --- VR, CVP or blood volume (hemorrhage) → --- their discharge.

Innervation: branches of vagus

Function: "Atrial Volume Reflex": Stimulation of atrial volume receptors lead to:

a. Systemic VD

b. +++ Heart rate

Physiological role: pumping of +++ VR without marked +++ in preload. It prevents blood accumulation in atria & pulmonary vessels (pulmonary edema)

Bainbridge Reflex:

Rapid infusion of large volume of blood or saline in anaesthetized animals → +++ HR if the initial HR is slow (If the initial HR is high, the reflex is abolished)

N.B.: +++ atrial receptors → ---- vasopressin, ---- renin & ---- aldosterone & +++ ANP → intermediate-time course and long-term regulation of ABP (see later).

III. Peripheral chemoreceptors

Effect of changes in blood gases on ABP:

A- Stimulation of peripheral chemoreceptors:

Site: carotid and aortic bodies.

Innervation: Carotid sinus nerve from carotid bodies and vagus from aortic bodies.

Stimulation:

1. Primarily concerned with respiratory regulation
2. Marked --- in ABP (40-60 mmHg) → --- blood flow in carotid, aortic bodies → hypoxia → +++ of peripheral chemoreceptors.

Response:

+++ Peripheral chemoreceptor → tachycardia (+++ HR) and VC → tends to +++ ABP

Mayer waves: Cyclic fluctuations in ABP (once/20-40 sec in hypotensive patients).

Hypotension → ischemia & +++ of peripheral chemoreceptors → +++ ABP → +++ blood flow to peripheral chemoreceptors → no stimulus → --- ABP & cycle repeats itself.

B- Effect through medullary cardiovascular centers:

Hypercapnia mainly, and hypoxia, can directly stimulate VMA → +++ ABP.

The Central nervous system (CNS) ischemic response:

- The reflex is the most powerful stimulus of sympathetic nervous system.
- --- ABP < 50 mmHg → brain ischemia → +++ CO_2 → +++VMA → VC → +++ ABP

Cushing reflex: +++ intracranial pressure (ICP)→ marked +++ of ABP & bradycardia

Mechanism: High ICP compresses cerebral bl vs → brain ischemia → +++ CO_2 & --- O_2 → +++ VMA → +++ ABP → +++ baroreceptors → --- HR (bradycardia)

B- Intermediate Time Course Mechanisms *(min to few hrs)*

I. Stress Relaxation:

- It is the decline in pressure over time at constant volume:

+++ blood volume → initial +++ in pressure inside blood vessels. Over minutes, it gradually decreases to stabilize at a lower value.

- It is due to <u>viscoelastic properties</u> of blood vs and not to their contractile properties.
- It is due to <u>--- wall tension</u>

<u>Importance: Defense against sudden changes in blood volume on ABP as follows:</u>

a- **<u>+++ blood volume</u>** → +++ MSFP, VR, COP & then ABP. Stress relaxation → --- MSFP & minimize the effect of +++ blood volume on ABP.

b- **<u>Sudden — in blood volume</u>** → --- MSFP, VR, COP & ABP. Stress relaxation → +++ MSFP & minimize the change in VR, COP & ABP.

II. Capillary Fluid Shift Mechanism:

<u>It minimizes the effect of changing blood volume on ABP as follows:</u>

a- +++ blood volume → +++ ABP & +++ capillary hydrostatic pressure → more filtration→ --- blood volume → --- VR & COP → minimize the rise in ABP

b- --- blood volume → --- ABP & --- capillary hydrostatic pressure → movement of fluid into capillaries → +++ blood volume → +++ VR & COP → minimize the drop of ABP.

III. Renin-Angiotensin System (RAS):

i. --- ABP & hypovolemia → +++ renin release from JGA in kidneys.

ii. Hepatic angiotensinogen <u>renin →</u> Ang-I <u>(ACE) →</u> Ang-II

iii. Activation of RAS and formation of angiotensin II takes about 20-30 minutes.

iv. Angiotensin II → +++ ABP by direct VC & by activation of sympathetic discharge.

C- Long Term Regulation of Arterial Pressure *(days)*

Renal-Body Fluids Mechanism (adjust ECF volume)

<u>I- Renal pressure natriuresis:</u>

<u>Basic and most important mechanism for long-term regulation of ABP:</u>

a- +++ ABP → +++ renal excretion of Na^+ & water → pressure natriuresis → --- ECF volume & ABP. Pressure natriuresis continues until --- ABP to normal level.

a- --- ABP (hemorrhage) → --- renal Na^+ & H_2O excretion → minimize the ---- of ABP.

<u>II- Renin-angiotensin-aldosterone system:</u>

1- --- ABP → +++ rennin → angiotensin II → long-term regulation of ABP through:

a- --- Na^+ and water excretion by the kidneys.

b- +++ aldosterone → +++ Na^+ & H_2O reabsorption → +++ ECF volume → +++ ABP

2- +++ ABP → --- angiotensin II & aldosterone → +++ Na^+ & H_2O excretion → --- ECF volume → ---- ABP back to normal.

➢ Inhibition of RAAS enhances the activity of pressure natriuresis mechanism.

<u>III- Atrial natriuretic peptides (ANP) secretion:</u>

➢ ANP enhances the activity of pressure natriuresis mechanism.

+++ ECF volume → stretches atrial muscle → ANP → +++ Na^+ excretion → --- ECF volume & ABP to normal.

IV- Vasopressin secretion:

--- ECF volume → --- atrial receptors → +++ vasopressin → --- H_2O excretion by kidneys → prevent further --- in ECF volume & ABP.

Circulatory Shock

State of inadequate tissue perfusion with relatively or absolutely inadequate COP. **Types:**

Hypovolemic:	Low-resistance:	Cardiogenic:	Obstructive:
--- blood volume	marked VD, while normal blood volume	----myocardial pumping →--- CO	significant obstruction to blood flow to/from heart
a. Hemorrhage b. Trauma c. Dehydration: vomiting, diarrhea d. Surgical shock: external / internal bleeding	a. Neurogenic shock: (strong emotions) b.Anaphylactic shock allergy→+++histamine c. Septic shock: severe infection → toxins	a.Myocardial infarction: --- contraction → ---CO b.Arrhythmias: rapid arrhythmia → --- filling Very slow arrhythmias	a. Pneumothorax b. Pulmonary embolism c. Cardiac tamponade: +++pericardial fluid d. Tight stenosis of cardiac valves

Hemorrhagic Shock

Manifestations:

1- Rapid pulse (reflex +++ sympathetic activity);;; low pulse pressure.
2- Hypotension (--- VR & COP).
3- Pale cold (cutaneous VC) clammy skin (+++ sympathetic → +++ sweat secretion).
4- Thirst (angiotensin II and baroreceptors-mediated response).
5- ----- urine (oliguria) due to --- renal blood flow.
6- Rapid respiration (+++ of peripheral chemoreceptors).
7- Acidosis (tissue hypoxia → anaerobic glycolysis & +++ lactic acid).
8- Restlessness & apprehension (+++ catecholamines → +++ brain).
9- Deteriorated consciousness → coma (acidosis & cerebral ischemia).

Compensatory reactions to hemorrhagic shock:

I- Rapid Compensatory Reactions to Hemorrhage:

To maintain ABP & normal blood supply to the brain & myocardium

A. Neural Mechanisms:

1- --- ABP → --- arterial baroreceptors

2- --- blood volume → --- atrial volume receptors

3- --- blood flow rate → +++ peripheral chemoreceptors

These changes → +++ medullary VMA → +++ sympathetic → +++ ABP as follows:

1- +++ HR & force of myocardial contraction → +++ COP & ABP

2- VC of arterioles → +++ TPR and ABP

- VC of skin vessels → cold and pale
- VC of renal vessels → ---- glomerular filtration rate & urine volume (oliguria)
- VC of renal vessels → damage of renal tubules and renal failure
- Coronary vessels are dilated due to +++ cardiac work
- Cerebral vessels are not constricted → maintained cerebral blood flow

3- VC of veins → ++ MSFP → ++ VR → better ventricular filling & ++ COP → ++ ABP

+++ peripheral chemoreceptors → +++ respiration → help +++ VR → +++ COP & ABP.

B. Humoral Mechanisms:

1. **Catecholamines secretion:**
   a. +++ catecholamines from adrenal medulla & sympathetic noradrenergic fibers
   b. Limited role of catecholamines in raising ABP

Catecholamines → +++ reticular formation of brain stem → +++ respiration & restlessness

2. **Angiotensin II:** +++ renin → +++ angiotensin II:
   - Vasoconstriction.
   - +++ thirst sensation → Drinking
   - Stimulation of aldosterone secretion.
3. **Vasopressin:** --- atrial volume receptors → +++ vasopressin → +++ water retention

II- Long-Term Compensatory Reactions:

To restore blood volume, ABP can be maintained normal with normal blood flow to all tissues

1- Correction of plasma volume: 12-72 hr after moderate hemorrhage, through:

a. **Tissue fluid shift**: Hemorrhage → --- capillary hydrostatic pressure → interstitial fluid moves into capillaries & +++ plasma volume

b. **Thirst sensation.**

c. **Aldosterone secretion:** → +++ Na^+ & H_2O reabsorption

d. **Vasopressin** (ADH) secretion → --- water excretion by kidneys

2- Correction of Plasma Proteins: 3-4 days

a. Preformed albumin enters blood from extravascular stores.

b. Hepatic synthesis of plasma proteins → complete restoration

3- Correction of Red Cell Mass: 4-8 week to restore RBCs to normal

Hemorrhage → hypoxia of kidneys & liver → +++ erythropoietin → +++ RBCs formation